Disclosures

- I have no relevant financial disclosures
- When a patient has not gotten better and comes to see me, if there is no evidence based treatment with good data, I prefer doing something rather than nothing, as they have already had nothing and it is not working.
- This experience may influence my discussion
- I will probably say lots of off-label things about psychotropics-lots!
Classification of Drugs

- Chemical class
- Origin-plant family
- Condition usually treated
- Physiologic actions (sympatholytic, mimetic)
- Receptor activity
- Mechanism of action
  - Agonists, antagonists, partial agonists, reverse agonists
  - Muscarinic, nicotinic,
  - Reuptake blocker, precursor

Classification by Condition

- Major depression-antidepressants
- Bipolar disorder-mood stabilizers
- Schizophrenia-antipsychotics
- Anxiety disorders-antianxiety
- Insomnia-hypnotics
- ADHD-stimulants/other
- Dementia-cognitive enhancers

Classification by Drug Class-Tricyclic Antidepressants

- Major depression
- Generalized anxiety disorder
- Social phobia
- Obsessive-compulsive disorder
- Panic disorder
- Post-traumatic stress disorder
- Body dysmorphic disorder
- Anorexia and bulimia
- Attention-deficit hyperactivity disorder
- Parkinson's disease
- Chronic pain
- Migraine
- Tourette syndrome
- Irritable bowel syndrome
- Interstitial cystitis
- Nocturnal enuresis
- Narcolepsy
- Insomnia
- Pathological laughter
- Chronic hiccups
Psychopharmacology in the Clinic

- Rational therapeutics starts with diagnosis
- Pathophysiologic target and disease eradication
- Replacement
- Syndrome suppression
- Symptomatic suppression
- Cosmetic therapy

Psychiatry

- Rarely has a specific disease to eradicate
- Replacement is uncommon
- Few syndromes
- Mostly symptom suppression
- Too much cosmetic psychiatry

Therapeutic vs Symptomatic
(In psychiatry we need to beware cosmetic psychopharmacology)

**Therapeutic**
- Drug effects try to counter or correct pathology
- Goal is to improve function
- Antidepressants
- Neuromodulators

**Symptomatic**
- Drugs block or activate pathways that produce symptoms
- Goal is to make people feel better
- Anxiolytics
- Opiates
Antidepressants-uses

- Major depression
- Panic attacks-most
- Chronic pain-TCA and SNRIs
- GI disturbance-TCA inhibit, SSRI activate
- Migraine-TCA and some atypicals, SNRIs
- OCD-SSRI, SNRIs, some TCA
- Attention deficit-TCA
- Generalized Anxiety-SSRI, SNRIs, TCA

Antidepressant-classes

- Tricyclic Antidepressants
- Monoamine Oxidase Inhibitors
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- SNRIs
- Bupropion
- Mirtazapine
- Trazodone and Nefazodone (Vilazodone)
- Maprotiline
- Vortioxetine

Depression

- Stress
- Demoralization
- CNS inflammation
- Substance abuse
- Subcortical injury
- Cognitive impairment

HIV/Hep C

- Impulsivity
- Hopelessness
- Carelessness
- Demoralization
- Substance abuse
- Cognitive impairment
Pharmacotherapy For Depression

- Poor sleep
- Weight loss
- Anxiety
- G.I. disturbance

Desipramine
Nortriptyline
(other TCAs) (Maprotiline)

- Hypersomnia
- Weight gain
- Suicide potential
- Chronicity

Augmentation
Antipsychotics, Thyroid, Pindolol, Lamotrigine, Dopamine agonists

Two Ways to Think About Depression

Categorical
Demoralization (Sadness/Grief) → Major Depression

Dimensional
Demoralization (Sadness/Grief) → Severity

Mean Standardized Improvement as a Function of Initial Severity

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.


**Proportion of Patients Responding**

- **Patients With ≥50% Improvement on SSRI, TCA, or Placebo**

**Publication Year**
- Placebo (n=75)
- TCA (n=43)
- SSRI (n=33)

**Patients With ≥50% Improvement**

**Placebo vs 10 mg of Escitalopram**

**FIGURE 1**. MADRS improvement over time in both placebo and treatment group.

**Tricyclic Antidepressants (TCAs)**
- Imipramine and Amitriptyline (late 1950s)
- Nortriptyline, Desipramine, Doxepin, Protriptyline
- Need blood levels (but they predict therapy)
- Alpha blocking, Antimuscarinic
- Cause sedation, weight gain, dry mouth, constipation
- Cardiotoxicity (dangerous in overdose)
- EKG in overdose predicts lethality
Tricyclic Antidepressants (TCAs) Common Uses

- Chronic pain
- Neuropathy
- Post-herpetic neuralgia
- Migraine
- GI spasm
- Diarrhea
- Insomnia (doxepin)

SSRIs (Black Box for Suicidal Ideas)

- Fluoxetine - long half life, little sedation
- Sertraline - GI activating
- Paroxetine - sedating, weight gain, short half life (beware withdrawal syndrome) (CR formulation)
- Fluvoxamine - indication for OCD
- Citalopram - less activating but not sedating (black box for QT)
- Escitalopram - isomer of citalopram

SSRIs

- Akathisia - restlessness, different than neuroleptics, very unpleasant, a suicide risk?
- Anorgasmia - decreased sex drive
- Apathy
- Suicidality? Children and Adolescents? Old data on antidepressants and activation
SSRIs Common Uses
- Gastroparesis
- Chronic constipation
- Panic attacks
- Generalized anxiety
- OCD

SNRIs
- Similar to SSRIs
- Efficacy in chronic pain on a par with TCAs
  - Venlafaxine
  - Duloxetine
  - Desvenlafaxine
  - Milnacipran
  - Levomilnacipran

Bupropion
- Least sexual side effects
- Least sedating
- Decreases nicotine craving
- Decreases Etoh craving
- Sometimes good for ADHD
Heterocyclic Antidepressants

- Trazodone - very sedating, used mostly for sleep, effective for depression at high doses
- Nefazodone - specific liver toxicity, LSD like visual “trails” (great drug, no one uses it because of the liver issue)
- Vilazodone - ?

Mirtazapine

- Safer than TCAs with many similar advantages
- Sedation and improved sleep
- Pain efficacy
- Weight gain
- Did I mention weight gain?

Monoamine Oxidase Inhibitors (MAOIs)

- Tyramine poisoning
- Serotonin syndrome
For Newer Antidepressants

- Drug trials only have to be better than placebo at 9-12 weeks
- The trials are underdosed (in my opinion) and patients need higher doses, particularly for pain

Other Drugs and Conditions that Everyone Will Encounter

Psychosis

- Distinguish between delirium and psychotic states
- Delirium-waxing and waning, poor ability to attend, change in the level of consciousness, almost always organic and needs urgent workup
- Psychosis-almost always a product of schizophrenia, bipolar disease or depression, and in clear consciousness
Agitation

- Must develop a differential diagnosis: delirium, psychosis, unreduced week old hip fracture, hunger, constipation

Antipsychotics-Neuroleptics

- Used in
  - Schizophrenia
  - Bipolar and depression induced psychosis
  - Sedation for agitation
- First generation ("typical") (D-2 blockers)
- Second generation ("atypical")

Schizophrenia

- Affects 1-2% of the world’s population
- 3.2 million Americans
- 25% of all mental health costs (US)
- One third of psychiatric hospital beds
- U.S. $62.7 billion 2002
  - $22.7 billion excess direct health care costs
  - $7.0 billion outpatient
  - $5.0 billion drugs
  - $2.8 billion inpatient
  - $8.0 billion long-term care
Neuroleptic Side Effects
(Less in Newer Drugs-Not None)

- EPS: Acute dystonic reactions, akathisia, parkinsonism
- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Seizures, dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, slowed cardiac conduction, hyperprolactinemia, weight gain, predispose to heat stroke, photosensitivity, lupus-like reactions, cholestatic jaundice, agranulocytosis

Problems with Neuroleptics

- Poor patient adherence/acceptance
- Weight gain
- Insulin resistance (and other markers of metabolic disorder)
- Increased lipid levels
- QT prolongation
- Sedation
- Akathisia
- Apathy
- Cognitive impairment (patients describe a zombie-like effect)
- Dystonia and movement difficulty (Parkinson's-like features)
- Marked differences in therapeutic effectiveness that is patient specific

Atypical Neuroleptics

<table>
<thead>
<tr>
<th>Atypical Neuroleptics</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Agranulocytosis, weight gain, alpha blockade, sedation, delusion</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Weight gain, dystonia, nausea, vomiting</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Weight gain, sedation, weight gain, weight gain, insulin resistance</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Sedation, transaminase, constipation, weight gain, insulin resistance</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Less sedation, little weight gain, more motor effects</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Less sedation but short half life, salivation only</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Less sedation, better tolerated?</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Too new</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Less sedation, better tolerated?</td>
</tr>
<tr>
<td>Iloperidone</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td></td>
</tr>
</tbody>
</table>

5/2/2016
Managing Side Effects

- Acute dystonia: Diphenhydramine 25-50 mg I.V., benztpine mesylate 1-2 mg I.V. or I.M.
- Akathisia: unpleasant sensation of motor restlessness most in legs, pts may appear agitated or pace, careful not to mistake it for worsened psychosis- beta blockers or benzo
- Parkinsonism: oral anticholinergics or dopamine agonists (amantadine)
- Tardive dyskinesia: risk factors- elderly, female, diabetic, high dosage, long duration treatment, concomitant mood disorder.

Injected Long-Acting Antipsychotics

- Fluphenazine decanoate (fluphenazine)
- Haloperidol decanoate (haloperidol)
- Risperidone microspheres (risperidone)
- Olanzapine pamoate (olanzapine)
- Aripiprazole extended release (aripiprazole)
- Aripiprazole lauroxil (aripiprazole lauroxil)
- Paliperidone palmitate, 4-week (paliperidone)
- Paliperidone palmitate, 12-week (paliperidone)

Neuroleptics vs Benzodiazepines for Agitation

- Few studies of benzodiazepines show efficacy for treatment of agitation
- The positive studies mostly used the endpoint of sedation
- The use of benzodiazepines for agitation remains contentious
- Many studies show that it is possible to decrease neuroleptic dose with benzo augmentation
The Drugs Everyone Wants

- There are drugs with less than 100% compliance and drugs with more than 100% compliance
- This is the 2nd group
- Sedative-Hypnotics and anxiolytics
- Stimulants
- Opiates

Anti-Anxiety Agents (Sedative-Hypnotics)

- Alcohol
- Bromides (potassium bromide) mid 1800s
- Chloral Hydrate 1869
- Phenobarbital (1912)
- Meprobamate (1955)
- Chlordiazepoxide (1960)

Anti-Anxiety Agents (Sedative-Hypnotics)

- Non-specifically decrease anxiety (symptomatic rather than therapeutic)
- Produce euphoria and are positively reinforcing
- Produce tolerance, dependence and withdrawal
- Withdrawal can be life threatening
- Are “addictive”
- Are widely used for “cosmetic” reasons
- This includes the “z-drugs”
  - Zopiclone
  - Zolpidem
  - Zaspidere
Sedative Hypnotics

- Abortive for panic attacks but not good for chronic treatment
- Great for sleep but not good for chronic treatment
- These drugs are very useful when used sparingly
- It is very difficult to get the patient off of them

Stimulants

- I have ADHD and need my ...
- Stimulants are powerful reinforcers
- ADHD is a real disorder, but many patients get started on it for cosmetic reasons
- In clinical trials, TCAs and atomoxetine are as effective, but have no street value

What do I do when my patients are already on narcotics, benzodiazepines or stimulants?

- Gradual taper over a year
- Use the drug to increase function
- Sometimes you have to say no
- Get expert advice when you get stuck
Increased Patient Satisfaction Correlates with Increased Mortality